REMARKS

1. General Matters

1.1. Claim Amendments

Claim 1 has been amended in three respects:

(1) the polypeptide must be "isolated"

(2) the recited splice variant must have the sequence set forth in any one of SEQ ID NOs:74-84, 93, 95-104 or 109-110 (cp. Original claims 4 and 5; specification at P7, L22-29 and P8, L1-7, and see also pp. 8-11 and Table 4 on p. 33).

(3) the truncated EGF domain must have only the first four of the six conserved cysteines found in an intact EGF domain, and the fourth of those cysteines must be the penultimate amino acid at the C-terminus of the polypeptide.

We note that under In re Johnson, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977), there is written description for a "reduced genus" with specific embodiments excised (such as SEQ ID NOs:73 and 111-121 from original claims 4 and 5), in particular when the excised embodiments had previously been explicitly enumerated, as is the case here. See MPEP 2173.05(i), last paragraph. As can be seen from table 4, all of the retained sequences are Class I variants.

1.2. Election/Restriction

The Examiner states that since "applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse". Applicants did in fact make specific criticisms of the restriction requirement, i.e., that the restriction requirement did not make it clear whether it was a requirement for election of species (which is withdrawn if a generic claim is held allowable) or not.

A restriction may be traversed on the ground that it is incomplete or ambiguous.

We thank the examiner for clarifying that the requirement to elect one splicing variant is not a species election, but a distinct invention. This clarification is procedurally a new restriction, and we traverse on the ground that the different claimed splicing variants are related. The prior election is maintained.

The PCT rules do allow for examination of multiple products when there is "a technical relationship among those inventions involving one or more of the same or corresponding technical features". PCT Rule 13.2. Thus, there is "no [unity] problem in the case of a genus/species situation where the genus claim avoids the prior art", even though multiple species are claimed. PCT Administrative Instructions, Annex B, paragraph (c)(i).

As is evident from comparing amended claim 1 with Table 4, the splicing variants are now constrained to Class I.

We respectfully submit that Class I splicing variants for ErbB ligands qualifies as a genus. While certainly the sequences are different, that does not establish that they are unrelated.

Elected SEQ ID NO:81 is a Class I variant per pp. 33-34.

1.3. IDS

Applicants acknowledge that the listing of references in the specification (pp. 76-78) is not itself an IDS.

However, applicants have not relied on pp. 75-77 for that purpose. The attention of the examiner is respectfully directed to the IDS's filed February 26, 2008 and September 26, 2008, and on even date herewith.

1.4. Drawings

The examiner objects to Figs. 1, 2, 3, 4, 5B and 6 on legibility grounds. Substitute figures are enclosed, and conforming amendments have been made to the Brief Description.

We note that it is routine in the art, when presenting a sequence alignment, to use shading to indicate conserved residues and that shading is permitted in drawings. Presentation of text with a shaded background (for emphasis) is not prohibited per se. Nonetheless, we have replaced shading and highlighting with underlining and bolding to improve legibility.

It is respectfully submitted that the substitute figures are legible. It is noted that Figs. 4A and 4B replace Fig. 4 and 4 (continued), respectively. Also, Figs. 5B and 5C replace Fig. 5B. Although Fig. 5C presents subject matter previously presented in 5B, it is identified as a "New Sheet" because one sheet is being replaced with two and no sheet was previously labeled 5C. Fig. 6 presented two unlabeled views and these are now labeled 6A and 6B.

1.5. Specification

The objection to the specification for failure to contain a claim of priority to any application is improper. As noted by the examiner, a claim of priority under 119 (e) to 60/495,898 is presented in the ADS.

The Examiner's attention is respectfully directed to 37 CFR 1.76(a)(5) last sentence, which clearly indicates that it is not also necessary to present the claim of priority in the specification.

We thank the examiner for calling our attention to the embedded hyperlinks on page 64 (table 5) and at P69, line 11. We have inactivated these hyperlinks by deleting http:// and

ftp://, and this satisfies the policy considerations set forth in MPEP 608.01, i.e., preventing them being executed by a browser visiting the PTO website.

2. Statutory Subject Matter Issue (OA p. 6)

As suggested by the Examiner, claim 1 has been amended to recite that the protein is "isolated".

3. Written Description Issue (OA pp. 7-12)

Claims 1-4, 6, 8-14 and 13 stand rejected as allegedly failing to comply with the WD requirement.

With respect to the written description requirement, the Examiner has alleged that the claims are broad in that they encompass a large genus of polypeptides that are not sufficiently described in the specification. According to the Examiner, only splicing variants for which a sequence is specifically set forth in the specification meet the written description provision of 35 USC 112 (see last paragraph of page 11 of the Office Action). Thus, we believe that our amended set of claims overcomes this rejection, as it is limited to specific sequences (class 1 variants).

4. Enablement Issue (OA pp. 12-16)

With respect to the enablement requirement, the Examiner has alleged that the specification, while being enabling for an isolated polypeptide comprising a specific sequence (SEQ ID NO 81), does not reasonably provide enablement for the broad genus of polypeptides (see second paragraph of page 12 of the Office Action). We believe that the suggested claim amendments (limitation to specific sequences 74-84, 93, 95-104 and 109-110) overcome the enablement rejection as well. Plainly, there is no difficulty making the polypeptides, of

specified sequences, by conventional recombinant DNA techniques. Rather the examiner expressed doubt that the claimed splicing variants would have activity and thereby satisfy the how-to-use branch of the enablement requirement. With respect to the "how-to-use problem", we would like to note that the present application relates to novel ErbB ligand splice variants that each comprises at least one altered component of the EGF domain that affects ligand-mediated ErbB receptor activation. It is mentioned that one of the possible mechanisms by which the variant EGF domain affects receptor activation is indirectly by means of ligand sequestration (please see page 6 lines 6-12 of the application). In addition, under the definitions of the terms "inhibitory ligand" or "antagonist" it is mentioned that the antagonist may function indirectly by binding to an activatory ErbB ligand, thus sequestering it from receptor-dependent activation (please see page 19 lines 18-24 of the application).

As described in the application, and also noted on the first paragraph of page 15 of the Office Action, the experimental results showed that the ligands mEGF(1-32) and hNRG2(1-32) did not potentiate mitogenesis of the BaF/3-EGFR cells, did not bind soluble ErbB1 and ErbB2 receptors, but bound to betacellulin, which is an activatory ligand of an ErbB receptor. We believe that these results provide evidence in support of an inhibitory activity of splice variants according to the present invention, through ligand sequestration.

Thus, we believe that the disclosure provides objective evidence that splice variants of the invention have the activity/function that is attributed to them, and enables their use.

5. Prior Art Issues

5.1. Claims 1, 2, 4, 6 and 8-14 stand rejected as anticipated by Loukianov (1997) (OA pp. 18-19).

Loukianov et al. teach that the cDNA encoding the SF HB-EGF contains a 94 bp insertion which is located between the two exons that encode the EGF unit. This insertion causes a frame-shift and the appearance of a shorter protein which contains the signal sequence, the pro-region, the heparin-binding domain and an altered EGF unit. Even though the resulting SF HB-EGF indeed comprises a sequence as set forth in SEQ ID NO: 81, the variant which is taught in Loukianov et al. contains a tail of additional 9 amino acids after the fourth conserved cysteine, whereas the HB-EGF variant of the present invention, as well as the rest of the currently claimed splice variants of ErbB ligands, end one amino acid after the fourth conserved cysteine. The present claims recite "an isolated polypeptide comprising a splice variant of an ErbB ligand.... having only the first four of the six conserved cysteines found in an intact EGF domain, and wherein the fourth cysteine in said truncated EGF domain is the penultimate amino acid at the C terminus of the polypeptide". Therefore, we believe that Loukianov et al. do not anticipate the instant invention as claimed in the amended set of claims.

5.2. Claims 1-3, 6, 8-14 and 32 stand rejected as anticipated by Eppenberger (1999).

The second cited reference, Eppenberger et al., teaches a variant of heregulin, HRG-γ, which is truncated in the EGF-like domain. Specifically, a stop codon interrupts the EGF-like domain after the fourth conserved cysteine, and the protein terminates one amino acid after that fourth cysteine. Eppenberger et al. teach that HRG-γ is identical in the amino

acid sequence to HRG-α and HRG-ß, except the truncation. The examiner notes that Eppenberger et al. teach the biological activity of HRG-γ, which was found to be unable to increase tyrosine phosphorylation of ErbB2 as compared to HRG-ß peptide. The Examiner alleges that inhibitory activities of HRG-γ would reasonably be considered to be inherent since it has the same structure as recited in the claims.

We would like to note that Eppenberger et al. teach that even though HRG-γ was found to be unable to increase tyrosine phosphorylation of ErbB2 as compared to HRG-ß peptide, it was found to stimulate cell growth (through intracellular pathways rather than through an ErbB receptor). The stimulatory activity of HRG-γ is discussed in several places of this citation, see for example, page 7 lines 34-35, page 11 lines 5-14 and the brief description of figure 5. In contrast to the teachings of Eppenberger et al., the present invention relates to variants having an inhibitory activity.

In addition, we would like to note that the amended set of claims is now drawn to specific sequences, rather than to all splice variants of ErbB ligands that end one amino acid after the fourth conversed cysteine, which are different from the splice variant described by Eppenberger et al. We also like to note that SEQ ID NO: 73, which is a sequence of a splice variant of NRG1 (a synonym to HRG) has been excluded from the claimed group of SEQ ID NOs, and the present claims now recite "an isolated polypeptide comprising a splice variant of an ErbB ligand with the sequence set forth in any one of SEQ ID NOS: 74-84, 93, 95-104, or 109-110..". Support

for the amendment can be found on page 13 of the application, paragraph 0118.

Respectfully submitted,

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